REMARKS

Following entry of this amendment, claims 1-42 are pending and being examined on their merits. Claims 43-66, which stood withdrawn from consideration as being drawn to a non-elected invention, are cancelled with this response.

Applicants thank the Examiner for extending the courtesy of a telephonic interview to their representatives on April 26, 2004, the substance of which is summarized in an accompanying Interview Summary. Applicants believe the claims as amended in accordance with the Examiner's suggestions are now in condition for allowance, and they solicit a Notice of Allowance indicating such at the earliest possible time.

Rejection under 35 U.S.C. § 112

Claims 1, 2, 4-8, 10-16, 18-24, 26-34, 36-39, 41, and 42 stand rejected under 112 second paragraph as allegedly being indefinite for the recitation of a "batimastat compound." Applicants have amended the claims as suggested by the Examiner to overcome the rejection. Applicants submit the amendment renders the rejection moot and request withdrawal of the rejection.

Rejection under 35 U.S.C. 103

Claims 1-42 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over US 5,767,153 and WO 97/41844 or US 5,763,621.

In the Office Action dated March 8, 2004 the Examiner maintained the rejection holding Applicants' arguments to be non-persuasive. The Examiner's position is apparently that the cited art teaches the motivation to substitute the compositions of the primary reference into the

secondary references is found in the primary reference, which allegedly teaches "inclusion of a medicament in an emulsion with a lightly crosslinked polymer (polycarbophil) (citation omitted) for administration to the eye promotes the medicaments' bioavailability." Applicants respectfully submit that, even if the alleged motivation to combine the references did exist, the combination of references fails to render the instant invention obvious for at least the reason that neither the '41844 application nor the '621 patent reference teach the treatment of retinal neovascularization by topical administration of a batimastat compound to the eye. Applicants maintain that the '41844 and '621 references upon which the Examiner relies, fail to teach or suggest either a method for treating or preventing retinal neovascularization, in a mammal in need of such treatment, comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina. Moreover, it is only Applicants' disclosure that teaches a "batimastat compound" topically administered to the eye can reach the retina as shown in Figure 5.

In response to Applicants' arguments that the cited art failed to teach or suggest methods for treating retinal neovascularization by topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina, it was asserted in the March 8, 2004 Office Action that the claims do not specify delivery to the retina or alternatively that delivery "might be an inherent effect of the one step method of administering to the eye." In addition, the Examiner alleged that the '41844 reference teaches the treatment of retinopathies and since it teaches a method of topical administration "it is assumed that the inference is that the medicament is expected to reach the retina in the absence of evidence to the contrary." Office Action dated March 8, 2004 at page 4. Further, the

Examiner alleges that the '621 patent teaches topical administration to the eye of batimastat for the treatment of proliferative retinopathies. Office Action dated March 8, 2004 at page 4.

Applicants respectfully submit that the allegation that the claims do not specify delivery to the retina is misplaced. Each of the independent claims under examination recites methods of treating or preventing retinal neovascularization comprising topically administering to the eye a composition capable of delivering a therapeutically effective amount of a batimastat compound to the retina.

The allegation that delivery to the retina "might be an inherent effect of a one step administration to the eye" is also misplaced. No evidence to demonstrate that the skilled artisan would have expected "batimastat compounds" to cross the sclera and reach the retina has been presented in any Office Action. The Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103, *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988), in which there must be some suggestion or motivation to modify or combine references and there must be a reasonable expectation of success, *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion or motivation to make the claimed combination, and the reasonable expectation of success, must be found in the prior art, and not based on the Applicant's disclosure. *In re Vaeck*, 947 F.2d at 493. Applicants respectfully submit that in the absence of evidence to demonstrate that the skilled artisan would have expected a batimastat compound to cross the sclera and reach the retina the rejection must be withdrawn.

Any allegations regarding the teachings of the '41844 reference, discussed above, are belied by the fact that it is only "assumed that the medicament is expected to reach the retina" when applied by topical administration. Office Action dated March 8, 2004 at page 4 (emphasis

added). Applicants respectfully submit that the '41844 reference fails to teach that batimastat is expected to reach the retina when applied on the contralateral side of the sclera, and that the specific portions of the disclosure relied on in the Office Action dated March 8, 2004, Examples 1 and 2, are neither specifically directed to batimastat nor to retinal neovascularization. Moreover, Example 1 fails to specifically address neovascularization of the retina, a tissue which is not only on the contralateral side of the cornea and sclera from which a topical therapeutic is administered but also in the posterior segment of the eye.

The allegations made regarding the teachings of the '621 patent similarly fail to support a holding of obviousness over the claims of the instant invention. In the previous response, Applicants argued that, whatever else the '621 patent teaches with regard to the treatment of neovascularization, the reference fails to address the treatment of retinal neovascularization with a batimastat compound, and that the '621 patent acknowledged the poor bioavailability of batimastat.[1] In addition, Applicants argued that the '621 patent teaches away from the instant claims. In response to Applicants' arguments it was alleged in the Office Action of March 8, 2004 that the '621 patent supports a conclusion of obviousness based upon a passage generically discussing proliferative retinopathies in column 1 and a passage allegedly supporting topical administration in column 11. Applicants respectfully submit that these passages fail to address the treatment of retinal neovascularization by a topically administered batimastat compound, or to provide a reasonable expectation of success in such a treatment. While the '621 patent might teach the topical administration of metalloprotease inhibitors, it neither teaches nor suggests the

[1] Applicants specifically noted that the only passage of the '621 patent that discusses batimastat acknowledges its poor bioavailability upon oral administration. Column 3 lines 36-47.

use of "batimastat compounds" in the instantly claimed methods as acknowledged by the Examiner in the rejection. Because nothing in the '621 patent addresses the successful administration of batimastat compounds to the retina by topical administration to the eye, there is no basis on which a reasonable expectation of success in the delivery of batimastat to the retina via topical administration may be supported. Moreover, as previously indicated, the '621 patent acknowledges the poor bioavailability of batimastat, *supra*. Applicants respectfully maintain that the acknowledged poor bioavailability of batimastat, combined with the fact that the '621 patent solves the issue of poor bioavailability of hydroxamic acid protease inhibitors by preparing compounds that fall outside of the scope of "a batimastat compound," taken together, effectively constitute a teaching away from the use of batimastat topically administered to the eye to treat retinal neovascularization.

The Examiner further takes the position that the Geroski *et al.* reference made of record by Applicants stands for the proposition that, although less than 5% of a medicament topically administered to the eye reaches intraocular tissues, topical formulations remain effective. Applicants respectfully submit that the Geroski reference does not stand for this generic proposition, and that Geroski not only teaches that a majority of the medicament administered to the eye is generally **not** available to intraocular tissues, but that the "delivery of therapeutic doses of drugs to tissues in the posterior segment of the eye [, however,] remains a significant challenge." *See* Geroski *et al.* at page 961, column 1. Furthermore, Geroski expressly states:

> Topically applied drugs may enter the eye by crossing the conjunctiva and then defusing through the sclera, but for reasons previously cited, this approach typically does not yield therapeutic drug levels in the posterior vitreous, retina, or choroid, and although systemic administration can deliver drugs to the posterior eye, the large systemic doses necessary are often associated with significant side effects.

Id., at column 2. Applicants maintain that the Geroski reference supports their position that one of skill in the art would have no reasonable expectation that topical administration to the eye would be an effective means to accomplish delivery of a therapeutic amount of a batimastat compound to the retina, which is located in the posterior segment of the eye on the contralateral side of the sclera, and that this art-recognized difficulty is not addressed by the cited references.

For the foregoing reasons, Applicants submit neither a motivation nor a suggestion to combine the references exists in the cited art, and that a prima facie case of obviousness has not been established. Accordingly, Applicants respectfully request withdrawal of the rejection and solicit a Notice of Allowance at the earliest possible time for the reasons recited above, and for the reasons of record in Applicants' previous response, which is herein incorporated by reference.

CONCLUSION

In view of the foregoing Applicants believe the application is in condition for allowance and solicit a Notice of Allowance indicating such at the earliest possible time. The Examiner is encouraged to contact the undersigned should any additional information be necessary.

Respectfully submitted,

Joel M. Freed (Reg. No. 25,101)
Joseph W. Ricigliano (Agent Reg. No. 48,511)

Date: May 26, 2004

ARNOLD & PORTER LLP
555 Twelfth Street, NW
Washington, D.C. 20004
(202) 942-5000 telephone
(202) 942-5999 facsimile